REMARKS

The Final Office Action mailed January 29, 2009, has been received and reviewed. All claims stand rejected. Basis for the amendment to claims 2 and 36 is found throughout the specification, and more specifically at paragraphs [0014] and [0039]. The application is to be amended as previously set forth. No new matter has been added. Reconsideration is respectfully requested.

Personal Interview

This Amendment and Request for Continued Examination are being submitted in preparation for the personal interview scheduled for April 6, 2009.

35 U.S.C. § 103 Obviousness Rejections

Obviousness Rejections Based on Cassol *et al.*, *Journal of Clinical Microbiology*, 1997, 35(11):2795-2801 (hereinafter "Cassol 1997"), in view of Cassol, *et al.*, *Mem. Inst. Oswaldo Cruz, Rio de Janeiro*, 1996, 91(3):351-358) (hereinafter "Cassol 1996") and U.S. Patent 5,482,834 to Gillespie (hereinafter "Gillespie")

Claims 2 through 4, 6, 7, 17, 36, and 37 are rejected under 35 U.S.C. § 103(a) as allegedly being made obvious by Cassol 1997, Cassol 1996 and Gillespie. Applicants respectfully traverse the rejection.

A *prima facie* case of obviousness under 35 U.S.C. § 103(a) has not been established since one of ordinary skill in the art would not have been prompted to combine the applied references in the manner asserted by the Office. In addition, the combination of applied references actually teaches away from the presently claimed method. Finally, the applied references themselves, or the inferences and creative steps that a person of ordinary skill in the art would have employed at the time of the invention, would not have taught or suggested all the elements of the presently claimed method.

It is respectfully submitted that, without the benefit of hindsight, one of ordinary skill in the art would not have been prompted to combine the applied references in the manner asserted in the Office Action. Cassol 1997 is concerned with quantification of HIV RNA whereas Cassol 1996 only concerns sequencing and genetic characterization of HIV RNA. Cassol 1997 states

that dried blood spots had been used before, but only for non-quantitative research. See *Cassol 1997* at page 2795, second column. It is acknowledged in Cassol 1997 that the article teaches a different use of dried blood spots than previously described methods. Specifically, Cassol 1997 states that "we describe here the extension of filter paper-based methods to the quantification of viral RNA in dried plasma spots (DPSs) (emphasis added)." Accordingly, Cassol 1997 teaches that their research provides a novel use of dried blood spots. It is respectfully submitted that the novel use of dried blood spots in a quantification method for viral RNA would not have been obvious in view of previously described methods, such as those of Cassol 1996.

It is further submitted that one of ordinary skill in the art would not have been motivated to combine the teachings of Cassol 1997 and Cassol 1996 because Cassol 1997 concerns quantification, whereas Cassol 1996 concerns sequencing and genetic characterization of HIV. As is known in the art, and set forth in the applied references, methods of sequencing RNA, such as the method of Cassol 1996, require markedly different conditions than methods of quantifying RNA, such as the method of Cassol 1997. For example, when total RNA is quantified, essentially the total amount of RNA in a sample must remain intact. This, however, is not necessary in methods of sequencing RNA. Instead, much of the RNA is allowed to be degraded during the process so long as sufficient RNA remains in the sample to enable sequencing. The Office acknowledges that "the differences between quantifying RNA and sequencing RNA are well known to the ordinary artisan." *Final Office Action,* p. 7. Accordingly, one of ordinary skill in the art would recognize that methods for sequencing of HIV-1 RNA (i.e., Cassol 1996) and methods for quantification of total HIV-1 RNA (i.e., Cassol 1997) in a sample are distinct methods and, thus, are not readily interchangeable.

The Examiner states that "it is expected that [a 2000 microliter] sample size, or any sample size less than that (between 50 to 2000 microliters) would be acceptable for quantifying RNA." *Final Office Action*, at p. 7. However, at the priority date of the present invention, it was commonly taught in the art that only small volumes were suitable for quantification purposes. As provided in paragraph [0015] of the specification, high amounts of sample were not considered suitable for quantification because of observed inhibitory effects. Consistent with the knowledge in the art, Cassol 1997 teaches that the volume of the HIV Quantification Standard is reduced from 100 to 25 µl in order to compensate for the smaller 50-µl volume of dried plasma

spot specimens. *See* Cassol 1997, page 2796, ¶3. It is noted that "[t]he totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP § 2145(X)(D)(3) (emphasis added). Since the art, including Cassol 1997, teaches against the use of large volumes of sample on a solid carrier for quantifying nucleic acid, one of ordinary skill in the art would not have had a reasonable expectation of success using larger samples sizes as asserted in the Final Office Action. It is further submitted that, because it was known in the art that using large volume samples caused undesirable saturation of amplification reactions, one of ordinary skill in the art would have found the results of the claimed method surprising or unexpected.

Cassol 1997 further emphasizes the use of small input samples (e.g., 50 µL) for dried plasma spots stating that "[q]uantification of RNA levels with DPSs will be particularly valuable in the neonatal setting, in which only minute amounts of sample are available." *Id.* at page 2800, lines 25-27. This further demonstrates that one of ordinary skill in the art would not have had a reasonable expectation of success in using larger volume dried plasma spot samples for quantification purposes at the time of the present invention. In discouraging the use of large volume samples, Cassol 1997 actually teaches away from the present invention.

In the Office Action, it is asserted that "[Cassol 1997] does not teach that quatification cannot be accomplished when using lager sample sizes." *See* Final Office Action, p. 8. It is noted that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S.Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that the combination is more likely to be nonobvious). Cassol 1997 teaches that amplification reactions may become saturated when using a sample having a large volume (i.e., 200-µl). *Cassol 1997,* at page 2799. Since Cassol 1997 suggests that using a large volume sample in an amplification reaction would potentially render the method inoperable, one of ordinary skill would have been led away from the method of claim 1. In view of the prejudice in the art, one of ordinary skill in the art would refrain from using a large volume while adjusting other parameters. Thus, it would not have been obvious to one of ordinary skill in the art to quantify a total amount of RNA in a spot comprising at least 100 µl of a sample based on Cassol 1997 and Cassol 1996.

Furthermore, Cassol 1997, Cassol 1996 and Gillespie, alone or in combination, do not teach or suggest all of the elements of claim 2. It is acknowledged in the Final Office Action that "[t]he Cassol 1997 reference does not teach the use of at least 100 microliters of sample for a single spot." *Final Office Action*, p. 3. Thus, Cassol 1996 is relied upon as teaching a method for the direct automated sequencing of HIV-1 field isolates that includes collection of 2000 microliters. See *id.* However, Cassol 1996 does not teach or suggest excising a spot that includes at least 100 μL of at least one sample or extracting nucleic acid from a spot that includes at least 100 μL of blood. Instead, Cassol 1996 teaches that 2 ml of blood was applied to filter paper and dried. From the filter paper, two 1 cm^2 circles were cut out and each circle was cut in half. Then, each half was placed into a 1.5 ml sterile microfuge tube and RNA extracted (see methods, page 355, second column, last paragraph). Therefore, Cassol 1996 does not teach extracting RNA from a sample that includes 2000 μl of dried blood. Rather, a sample that includes half of a 1 cm^2 portion of a paper on which 2000 μl of blood was applied was used for extracting RNA from the dried sample.

According to the manufacturer, the Schleicher & Schuell newborn blotter paper (formerly Schleicher & Schuell #903, now Whatmann 903) used in Cassol 1996 holds 80 μl of blood per one-half inch (r=0.635 cm) preprinted spot. See *Information Disclosure Statement (IDS)* submitted herewith. Accordingly, the amount of blood held in a 1 cm^2 circle, such as that disclosed in Cassol 1996, may be determined as follows:

Since area (A) = $\pi(\text{radius})^2$, then the area of the one-half inch spot = $\pi \times (0.635\ \text{cm})^2$

Thus, for a 1 cm^2 circle, the amount of blood = $(80\ \mu l \times 1 cm^2)/(\pi \times 0.635^2)$ or about 63.2 μl

In Patisaul et al., "Genistein Affects ERβ- But Not ERα-Dependent Gene Expression in the Hypothalamus," *Endocrinology*, 143(6):2189-2197 (2002), Schleicher & Schuell #903 paper is used. See *IDS* submitted herewith. On page 2190, last paragraph, of Patisaul et al., it is provided that two spots of each one-eighth inch (r=0.159 cm) hold 10 μl of blood. If two one-eighth inch spots hold 10 μl each, then the amount of blood held by a 1 cm^2 spot may be determined as follows:

Since $A = 2 \times \pi(0.159\ \text{cm})^2$, then for a 1 cm^2 circle = $10\ \mu l / (2 \times \pi(0.159)^2) = 63.0\ \mu l$

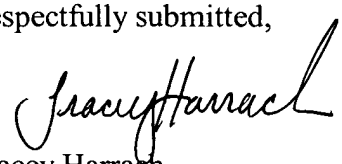
As previously discussed, Cassol 1996 teaches extracting RNA from half of a 1 cm^2 circle

punched out of the filter paper. As shown above, half of a 1 cm^2 circle may, hold 30 µl to 35 µl of dried blood. Cassol 1996, thus, does not teach a method that includes excising at least one spot comprising at least 100 µl of a sample from the surrounding filter paper and extracting nucleic acid from the at least one spot.

As Cassol 1997, Cassol 1996, and Gillespie do not teach or suggest excising at least one spot comprising at least 100 µl dried blood from a filter paper and extracting nucleic acid from the at least one spot, one of ordinary skill in the art would not have arrived at the presently claimed invention by combining the applied references in the manner asserted in the Final Office Action.

The application should now be in condition for allowance. If, however, questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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